

Two Patients Who Developed Leptospirosis-Associated Acute Renal Failure within the Same Season

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Abstract

In the autumn two patients with general malaise were consecutively admitted to the department of internal medicine of our hospital in the northern region of Nagasaki Prefecture. Since both patients were engaged in rice farm work and showed conjunctival suffusion and pain of the gastrocnemius muscle, leptospirosis was suspected. The first patient required temporary hemodialysis for renal dysfunction, whereas liver dysfunction developed in the second patient. The disease was remitted by antimicrobial agents. A diagnosis of leptospirosis was made serologically in both patients. Leptospirosis should be considered as a differential diagnosis when a patient engaged in farm work in the autumn has typical symptoms, and an early initiation of treatment after onset is important.

Key words: acute renal failure, autumn fever, conjunctival suffusion, leptospirosis, muscle pain

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Introduction

Leptospira is a Gram-negative aerobic bacterium that belongs to the Spirochaetaceae family and has a thin and long spiral body (diameter: 0.1 μm , length: 6-20 μm). Leptospirosis is a zoonosis in which various wild animals including rodents serve as maintenance hosts and humans are one of the accidental hosts. The latency period is about 3-14 days, with fever, chill muscle pain and headache suddenly developing as the initial symptoms in 75-100% of patients, and nausea, vomiting and diarrhea in 50% (1). Regarding physical findings, conjunctival suffusion is an important feature suggesting leptospirosis, since this condition is rarely seen in other infectious diseases. Tenderness of muscle; swelling of the spleen, lymph nodes and the liver; and skin erythema have been observed in 7-40% of patients with leptospirosis (2, 3).

The clinical course varies from a mild type, in which the

disease remits after development of common cold-like symptoms, to a severe type, which may be fatal due to multiorgan failure, including liver failure, hemorrhage, renal failure, uveitis, acute respiratory distress syndrome (ARDS), and rhabdomyolysis. The bacteria are transmitted to humans via exposure to urine of rodents (maintenance hosts), water and soil contaminated with this urine, or tissues of infected animals. The main routes of infection are via a skin abrasion, the mucosa, and the conjunctiva. A definite diagnosis can be made by detection of the pathogen in culture, by serological diagnosis in which an increase in serotype-specific IgG or IgM antibody titers of 4 times or more is found in paired sera, or by detection of the *Leptospira* gene by PCR.

Cases infected via exposure to contaminated water during waterside leisure and imported infection from epidemic regions such as the Central and South America and South-East Asia have increased with the recent increase in overseas travel. Moreover, import of leptospires into Japan via live-

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Table 1. Laboratory Test Results on Admission (Patient 1)

Blood					
WBC	14400 /mm ³	TP	6.5 g/dL	BUN	51.2 mg/dL
Seg	82 %	Alb	3.6 g/dL	Cre	5.61 mg/dL
Stab	4 %	T-bil	2.49 mg/dL	Na	136 mEq/L
Eosino	0 %	D-bil	1.5 mg/dL	K	4.0 mEq/L
Baso	0 %	AST	115 IU/L	Cl	97 mEq/L
Lympho	10 %	ALT	152 IU/L	CRP	30.2 mg/dL
Mono	4 %	LDH	705 IU/L		
RBC	422 X 10 ³ /mm ³	ALP	346 IU/L	PT	11.0 sec
Hemoglobin	13.2 g/dL	γGTP	144 IU/L	APTT	39.4 sec
Hematocrit	37.5 %	Amy	253 IU/L	Fib	679 mg/dL
Plt	9.6 X 10 ⁴ /mm ³	CPK	2228 IU/L	FDP	14 μg/mL
Urine					
Screening dipstick; albumin 4+, occult blood 1+					
Sediment; Red Blood Cells: 20-30/High Power Field, White Blood Cells: 30-50/High Power Field					

WBC:white blood cell, RBC:red blood cell, Plt:platelet, TP:total protein, Alb:albumin, T-bil:total bilirubin, D-bil:direct bilirubin, GOT:glutamic oxaloacetic transaminase, GPT:glutamic pyruvic transaminase, LDH:lactate dehydrogenase, ALP:alkaline phosphatase, γGTP:gamma-glutamyl transpeptidase, Amy:amylase, CPK:creatinine phosphokinase, BUN:blood urea nitrogen, Cre:creatinine, Na:sodium, K:potassium, Cl:chloride, CRP:C-reactive protein, PT:prothrombin time, APTT:activated partial thromboplastin time, Fib:fibrinogen, FDP:fibrin degradation product

stock animals and pets has been reported, which raises the concern of a future increase in the occurrence of leptospirosis as an imported infectious disease (4). As previously known, leptospirosis is called 'autumn fever' in Japan, since it is prevalent in the busy season for farmers, and more than 50 fatal cases were reported yearly until the early half of the 1970s. In Japan, Leptospirosis was added to the list of Group IV Infectious Disease in the revision of the Infectious Disease Law in November 2003. The number of reports of the disease in fiscal 2004-2006 was 17, 17 and 24, respectively, and the incidence during the farming season was high, accounting for 70.6-95.8% of cases (5). This indicates that many cases were caused by infection via exposure to water contaminated with *Leptospira* spp. (or leptospires) during this season. We encountered two patients who simultaneously developed leptospirosis-associated acute renal failure in the northern region of Nagasaki Prefecture, and here we describe these cases.

Case Report

Patient 1

The patient was a 47-year-old man who was engaged in rice farming and transport. He had opportunity for exposure to the water or soil contaminated by animal urine in a field work. He had no particular familial or past medical history. He performed farm work for about 1 week in late August 2004. General malaise and fever at 39°C developed in early

September, and he visited a physician and was given loxoprofen and carbocysteine under the diagnosis of a common cold. The symptoms remitted, but fever developed again. The patient visited the department of internal medicine in our hospital four days later and was treated with piperacillin for suspected bronchitis, but the symptoms did not improve. Renal and liver dysfunction and marked inflammatory reactions were noted in blood tests on the following day and the patient was admitted for close examination and treatment.

On admission, his consciousness was clear and he had a body temperature of 37.6°C; blood pressure, 100/70 mmHg; pulse rate, 78/min, regular; and mild hyperemia and jaundice in the conjunctiva. Heart and respiratory sounds were normal, intestinal noise was slightly reduced, and the liver and spleen were not palpable. Numbness of the left gastrocnemius muscle was noted, but no edema was present. On imaging, abdominal CT (echo) detected no abnormalities in the liver, gall bladder, or kidney.

The test findings on admission are shown in Table 1. Leptospirosis was suspected based on the patient's job (farm work) and clinical symptoms of conjunctival suffusion and jaundice and numbness of the gastrocnemius. Administration of piperacillin and streptomycin was initiated and fever temporarily decreased, but leukocytosis persisted. Thus, antibiotic administration was continued and fever started to decrease slowly on the 14th hospital day, with resolution of the symptoms, inflammatory reactions, and liver dysfunction.

Uremic symptoms, such as nausea, and acute renal failure

Table 2. Laboratory Test Results on Admission (Patient 2)

Blood					
WBC	11500 /mm ³	TP	5.8 g/dL	BUN	81.6 mg/dL
Seg	75 %	Alb	2.6 g/dL	Cre	3.82 mg/dL
Stab	3 %	T-bil	6.45 mg/dL	Na	133 mEq/L
Eosino	1 %	D-bil	4.8 mg/dL	K	3.8 mEq/L
Baso	0 %	AST	46 IU/L	Cl	97 mEq/L
Lympho	19 %	ALT	23 IU/L	CRP	36.0 mg/dL
Mono	1 %	LDH	536 IU/L	PT	12.1 sec
RBC	414 X 10 ³ /mm ³	ALP	709 IU/L	APTT	39.4 sec
Hemoglobin	13.2 g/dL	γGTP	61 IU/L	Fib	599 mg/dL
Hematocrit	39.4 %	Amy	292 IU/L	FDP	26.4 μg/mL
Plt	15.3 X10 ⁴ /mm ³	CPK	42 IU/L		

Urine	
Screening dipstick; albumin negative, occult blood ±	

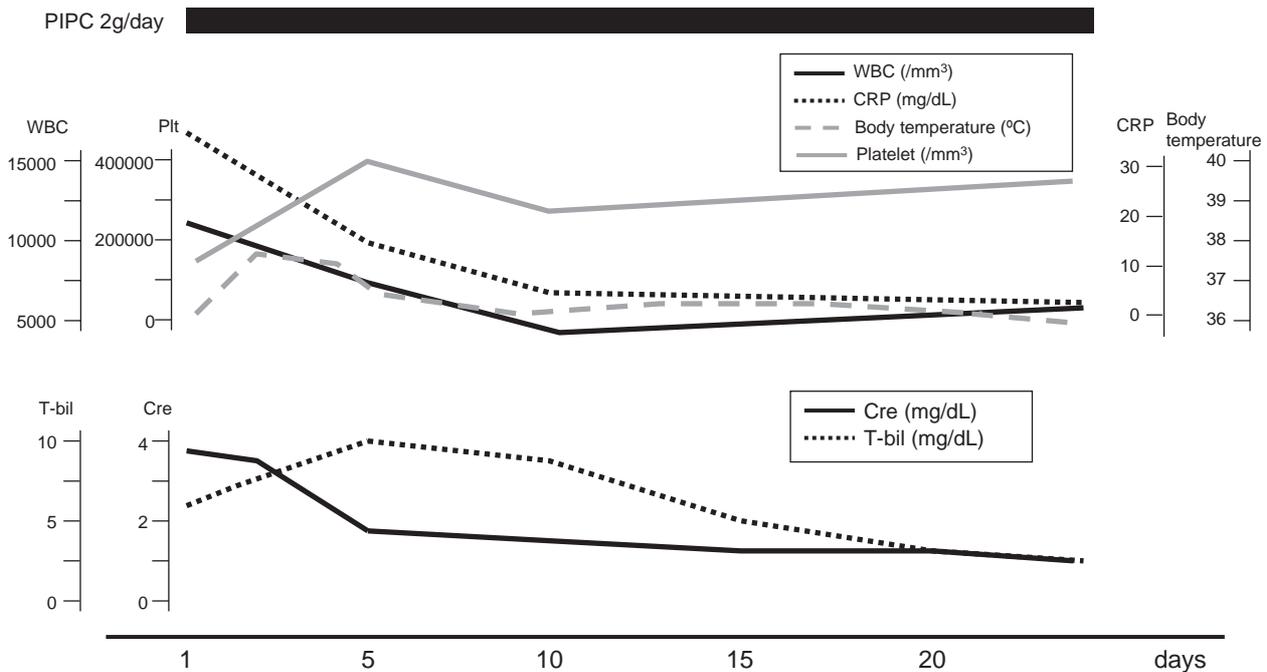


Figure 2. Summary of the clinical and therapeutic course (Patient 2).

tubulointerstitial nephritis with interstitial edema and mononuclear cell infiltration are main findings. It has been suggested that leptospiral outer membrane proteins may elicit tubular injury and inflammation through Toll-like receptor 2-dependent pathway followed by activation of nuclear transcription factor kappa β and mitogen-activated protein kinases and a differential induction of chemokines and cytokines relevant to tubular inflammation (6, 7).

Acute renal failure has been noted in 44-67% of cases of leptospirosis (8) and multiorgan failure in 5-10% (6). The mortality rate has varied from 4% to 52% among reports. Recently, doxycycline has been sporadically reported as the

antibiotic of first choice for treating leptospirosis (9), while on the other hand, penicillin has also been reported as the first choice therapy in patients presenting with serious forms of the disease (10). In these cases, although leptospirosis was suspected due to the characteristic clinical findings, because penicillin G was not used at our facility and doxycycline is only available in oral form in Japan, the penicillin-class drug piperacillin, which has been reported to be effective in the literature, was used at a dose adjusted for renal function (2 g/day). Blood purification has been suggested to be necessary for 74.1% of patients with leptospirosis who develop acute renal failure (11). Many cases of

leptospirosis-associated acute renal failure are non-oliguric and accompanied by hypokalemia, and the prognosis of oliguric cases is poor. Other prognostic factors include dyspnea, leukocytosis, electrocardiogram abnormalities, and pulmonary infiltration shadows.

In the present cases, the condition of Patient 1 was severe, with oliguria and leukocytosis, but leptospirosis was suspected on the first examination based on the characteristic clinical symptoms and physical findings, and treatment was initiated rapidly and may have saved the patient. Both patients may have been infected percutaneously when exposed to water contaminated with leptospires during farming. The patients worked on different river systems, but an association between the two cases was suspected because their residences were only about 6-km apart and the onset time was similar. However, the serotype corresponding to the elevated anti-*Leptospira* antibody was different, making it unlikely that the source of contamination was common.

Therefore, despite the two cases occurring during the same period they may not have been associated. There is no literature reporting the occurrence of leptospirosis in this region, and we believe there is value in reporting these occurrences.

Diagnosis of leptospirosis on the first examination is difficult in many cases because of its diverse symptoms. Moreover, the disease type varies from mild to severe. The progression is rapid in severe cases and may result in death due to renal failure and pulmonary hemorrhage.

With leptospirosis, the prognosis is improved by early diagnosis and treatment, and the objective of this paper is to relay the importance of making the appropriate diagnosis by spreading knowledge of the disease. It is very important to include this disease in those to be differentiated when a patient engaged in farming in the autumn visits a hospital for chief complaints of sudden fever and muscle pain, particularly when conjunctival suffusion is apparent.

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